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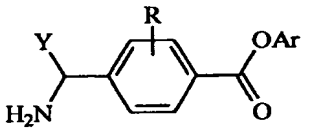

(I)

(57) Abstract

The invention relates to the use of compounds of formula (I) wherein R represents hydrogen, alkyl, alkenyl, hydroxy, alkoxy, aminoalkyl, hydroxyalkyl, carboxyalkyl, alkoxyalkyl, amino, halo, cyano, nitro, thiol, alkylthio, haloalkoxy or haloalkyl; Ar represents an optionally substituted carbocyclic or heterocyclic aryl group with the proviso that when Ar represents a naphthyl moiety it is not substituted by amidino or guanidine; and Y represents a hydrogen atom or alkyl group; or a physiologically tolerable salt thereof; for use as tryptase inhibitors.

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AMINOMETHYL-BENZOIC ESTER DERIVATIVES AS TRYPTASE INHIBITORS

The invention relates to compounds for use in the treatment of mast cell mediated diseases such as asthma and other allergic and inflammatory conditions and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body, and in particular to compounds which are tryptase inhibitors.

Asthma, the most prevalent of all mast cell mediated conditions affects about 5% of the population in industrialised countries and there is evidence that its incidence and severity are on the increase. Furthermore, the incidence of childhood asthma is rising and there are suggestions of a link between environmental pollutants and the onset of the disease.

Initially, it was believed that bronchoconstriction, i.e. the narrowing of the airways in the lungs, was the major feature of asthma. However, it is now recognised that inflammation in the lungs is an integral part of the development of the disease.

The inhalation of an allergen by an asthmatic generates a strong immune system response which triggers release of various inflammatory mediators, including histamine and leukotrienes from inflammatory cells. These increase the permeability of the blood vessel walls, attract inflammatory cells into the tissues and contract the smooth muscle around the airways. As a result, fluid leaks from the blood and the tissues swell, further narrowing the airways. The inflammatory cells cause damage to the epithelial cells lining the airways exposing nerve endings which stimulates secretion of mucous as well as augmenting the inflammation by causing the release of neurokinins.

Thus asthma is a complex disease frequently characterised by progressive developments of hyper-responsiveness of the trachea and bronchi as a result of

chronic inflammation reactions which irritate the epithelium lining the airway and cause pathological thickening of the underlying tissues.

Leukocytes and mast cells are present in the epithelium and smooth muscle tissue of the bronchi where they are activated initially by binding of specific inhaled antigens to IgE receptors. Activated mast cells release a number of preformed or primary chemical mediators of the inflammatory response in asthma as well as enzymes. Moreover, secondary mediators of inflammation are generated by enzymatic reactions of activated mast cells and a number of large molecules are released by degranulation of mast cells.

It has therefore been proposed that chemical release from mast cells properly accounts for the early bronchiolar constriction response that occurs in susceptible individuals after exposure to airborne allergens. The early asthmatic reaction is maximal at around 15 minutes after allergen exposure, recovery occurring over the ensuing 1 to 2 hours. In approximately 30% of individuals, the early asthmatic reaction is followed by a further decline in respiratory function which normally begins within a few hours and is maximal between 6 and 12 hours after exposure. This late asthmatic reaction is accompanied by a marked increase in the number of inflammatory cells infiltrating bronchiolar smooth muscle and epithelial tissues, and spilling into the airways. These cells are attracted to the site by release of mast cell derived chemotactic agents.

The most straightforward way of dealing with an asthma attack is with a bronchodilator drug which causes airways to expand. The most effective bronchodilators are the β-adrenergic agonists which mimic the actions of adrenalin. These are widely used and are simply administered to the lungs by inhalers. However, bronchoconstrictor drugs are primarily of use in short

term symptomatic relief, and do not prevent asthma attacks nor deterioration of lung function over the long term.

Anti-inflammatory drugs such as cromoglycate and the corticosteroids are also widely used in asthma therapy. Cromoglycate has anti-inflammatory activity and has been found to be extremely safe. Although such cromolyns have minimal side effects and are currently preferred for initial preventive therapy in children, it is well known that they are of limited efficacy.

The use of corticosteroids in asthma therapy was a major advance since they are very effective anti-inflammatory agents, however, steroids are very powerful, broad spectrum anti-inflammatory agents and their potency and non-specificity means that they are seriously limited by adverse side effects. Localising steroid treatment to the lungs using inhaler technology has reduced side effects but the reduced systemic exposure following inhalation still results in some undesirable effects. Hence, there is a reluctance to use steroids early in the course of the disease.

There therefore still remains a need for an alternative asthma therapy which is a safe, effective, anti-inflammatory or immunomodulatory agent which can be taken to treat chronic asthma.

Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation. Tryptase is one of a large number of serine protease enzymes which play a central role in the regulation of a wide variety of physiological processes including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. Although a large number of serine proteases have been widely investigated, tryptase still remains relatively unexplored.

Mature human tryptase is a glycosylated, heparin-

associated tetramer of catalytically active subunits. Its amino-acid structure appears to have no close counterpart among the other serine proteases which have been characterised. Tryptase is stored in mast cell secretory granules and after mast cell activation, human tryptase can be measured readily in a variety of biological fluids. For example, after anaphylaxis, tryptase appears in the blood stream where it is readily detectable for several hours. Tryptase also appears in samples of nasal and lung lavage fluid from atopic subjects challenged with specific antigen.

Tryptase has been implicated in a variety of biological processes, including degradation of vaso-dilating and bronchorelaxing neuropeptides thereby destroying potent bronchodilatory action and modulation of bronchial responsiveness to histamine. Accordingly, mast cell tryptase may increase bronchoconstriction in asthma by destroying bronchodilating peptides. Moreover, the ability of tryptase to activate prostromelysin and procollagenase suggests that tryptase also may be involved in tissue inflammation. Accordingly, tryptase has been proposed as a potentially important mediator in the development of inflammatory response in asthma and other inflammatory diseases. Accordingly, tryptase inhibition may be of great value in the propylaxis and treatment of a variety of mast cell mediated conditions, such as asthma, particularly in the treatment of chronic, late stage inflammatory asthma.

In WO96/09297, WO95/32945, WO94/20527 and US 5,525,623 a variety of peptide based compounds are suggested as potential inhibitors of the mast cell protease tryptase. In WO95/03333 a tryptase inhibitor is provided by a polypeptide obtainable from the leech *hirudo medicinalis*. In WO96/08275 secretory leukocyte protease inhibitor (SLPI) and active fragments thereof have been found to inhibit the proteolytic activity of

tryptase.

However, it has now been surprisingly found that certain aminomethyl-benzoic ester derivatives are particularly effective as inhibitors of tryptase and show a surprising selectivity for tryptase over other serine proteases.

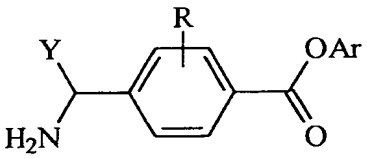
Aminomethyl-benzoic ester derivatives have previously been employed in a variety of fields. In US 5,628,803 aminomethyl-benzoic ester derivatives have been used as fuel additives. In EP 0048433, FR 2500825 and 2500826 a number of aminomethyl-benzoic ester derivatives are suggested as being useful in anti-complement compositions. The compounds are also said to have strong anti-trypsin, anti-plasmin and anti-kallikrein activity. In Japanese Abstract No. 57095908. aminomethyl-benzoic ester derivatives are disclosed as potential anti-allergic compounds and in Acta. Pharm. Nord. 3(1) 31-40 (1991) water-soluble aminoalkylbenzoate esters are suggested as prodrugs. In DE 1966174 and DE 1951061 a variety of aminomethyl-benzoic ester derivatives are suggested as having antiplasmin activity. However it has now been surprisingly found that certain aminomethyl benzoic ester derivatives are effective inhibitors of tryptase whilst showing a surprising selectivity for tryptase over other serine proteases such as Factor X, thrombin and trypsin.

Moreover, certain aminomethyl-benzoic ester derivatives have a prolonged biological stability, enhancing their usefulness when administered by a systemic route, such as orally or intravenously. While ester derivatives are generally poorly stable in biological systems, leading to a very limited duration of action in a therapeutic drug, stability to chemical and enzymatic hydrolysis can be enhanced by modification of the nature of the ester and/or by addition of stabilising chemical moieties. For example, the aminomethyl-benzoic ester derivatives of the present

invention may be substituted by a range of polar, in particular acidic, moieties that may yield a large increase in plasma stability.

It is envisaged that the compound of the invention will be useful not only in the treatment and prophylaxis of asthma but also of other allergic and inflammatory conditions mediated by tryptase such as allergic rhinitis, skin conditions such as eczema, atopic dermatitis and urticaria, rheumtoid arthritis, conjunctivitis and inflammatory bowel disease.

Thus, viewed from one aspect the invention provides the use of a tryptase inhibitor of formula I



(I)

wherein R represents hydrogen, alkyl, alkenyl, hydroxy, alkoxy, aminoalkyl, hydroxyalkyl, carboxyalkyl, alkoxyalkyl, amino, halo, cyano, nitro, thiol, alkylthio, haloalkoxy or haloalkyl;

Ar represents an optionally substituted carbocyclic or heterocyclic aryl group with the proviso that when Ar represents a naphthyl moiety it is not substituted by amidino or guanidine; and

Y represents a hydrogen atom or alkyl group;

or a physiologically tolerable salt thereof, e.g. a halide, phosphate, sulphate, or trifluoroacetate salt or salt with ammonium or an organic amine such as ethylamine or meglumine;

in the manufacture of a medicament for use in a method of treatment of the human or non-human animal body to combat a condition responsive to said inhibitor.

In the compounds of the invention unless otherwise stated, carbocyclic aryl groups preferably contain 5 to

10, more especially 5 or 6 ring atoms. Heterocyclic aryl groups preferably contain 5 to 10 ring atoms including 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur. Alkyl or alkenyl groups preferably contain up to 10 carbon atoms, most preferably, up to 6 carbon atoms.

The substituent R is preferably a short chain alkyl, e.g. C_{1-3} alkyl such as methyl but most preferably R represents hydrogen.

The substituent Y is preferably a short chain alkyl, e.g. C_{1-3} alkyl such as methyl but most preferably Y represents hydrogen.

Representative Ar groups include optionally substituted phenyl, optionally substituted naphthyl, optionally substituted pyridyl, optionally substituted quinolyl, and optionally substituted isoquinolyl. These groups should preferably carry at least one polar, especially acidic or protected acidic substituent.

In a preferred embodiment, the substituent on the carbocyclic or heterocyclic aryl group should not be strongly basic, i.e. ArH must be less basic than benzylamine. This ensures that the compounds of the invention bind more efficiently in the tryptase active site, thus maintaining selectivity.

Where Ar represents a phenyl derivative, the phenyl may be substituted by one or more substituents selected from: halo, for example fluoro, chloro, bromo or iodo, methylenedioxy, $-R^1$, $-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCO_2R^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w-Ph$, or R^1 and R^2 are optionally connected by a bond to form a 5-

8 atom cyclic structure (eg. piperidine) or connected via an O, S or N atom to form a 5-8 atom heterocyclic structure (eg. morpholine, piperazine) and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; R^3 is an oligomer comprising 1-4 aminoacid monomers, such as the natural aminoacids glycine, proline and serine, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2.

Preferably the substituent will comprise an electron withdrawing group and/or at least one polar moiety, most preferably an acidic or a protected form of an acidic moiety. Preferred electron withdrawing groups include cyano, nitro, carboxamido, alkylsulfenyl, alkylsulfonyl, alkylaminosulfonyl, sulphonylaminoalkyl, trifluoromethyl, or halogen, and most preferably where the substituent is an electron withdrawing group the substituent will be on the 2 or 4-position of the phenyl group.

The presence of at least one polar moiety, most preferably an acidic or a protected form of an acidic moiety (e.g. an ester) provides enhanced biological stability. Preferred acidic groups include alkyl or aryl carboxylic acids and esters, acyl sulphonamide, sulphonylamidocarboxyalkyl, carboxyamidosulphonylalkyl, tetrazole, sulphonic acid or phosphonic acid each bonded to the Ar ring directly or via an alkyl, sulphonamidoalkyl or carboxamidoalkyl linkage, the linkage itself being optionally substituted by small polar or apolar groups such as C_{1-4} alkyl, NH_2, CN, NO_2, NHCO-alkyl, or halogen. The acidic subsitutent will preferably be on the para position of the phenyl ring.

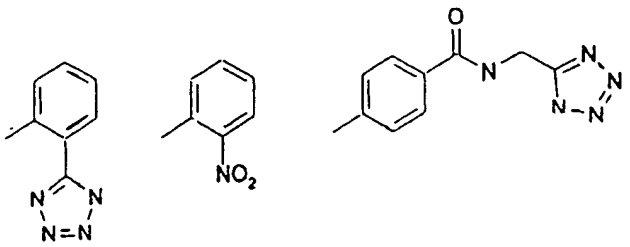
In another preferred embodiment an acidic substituent is present on the ortho position of the phenyl ring and a electron withdrawing substituent is

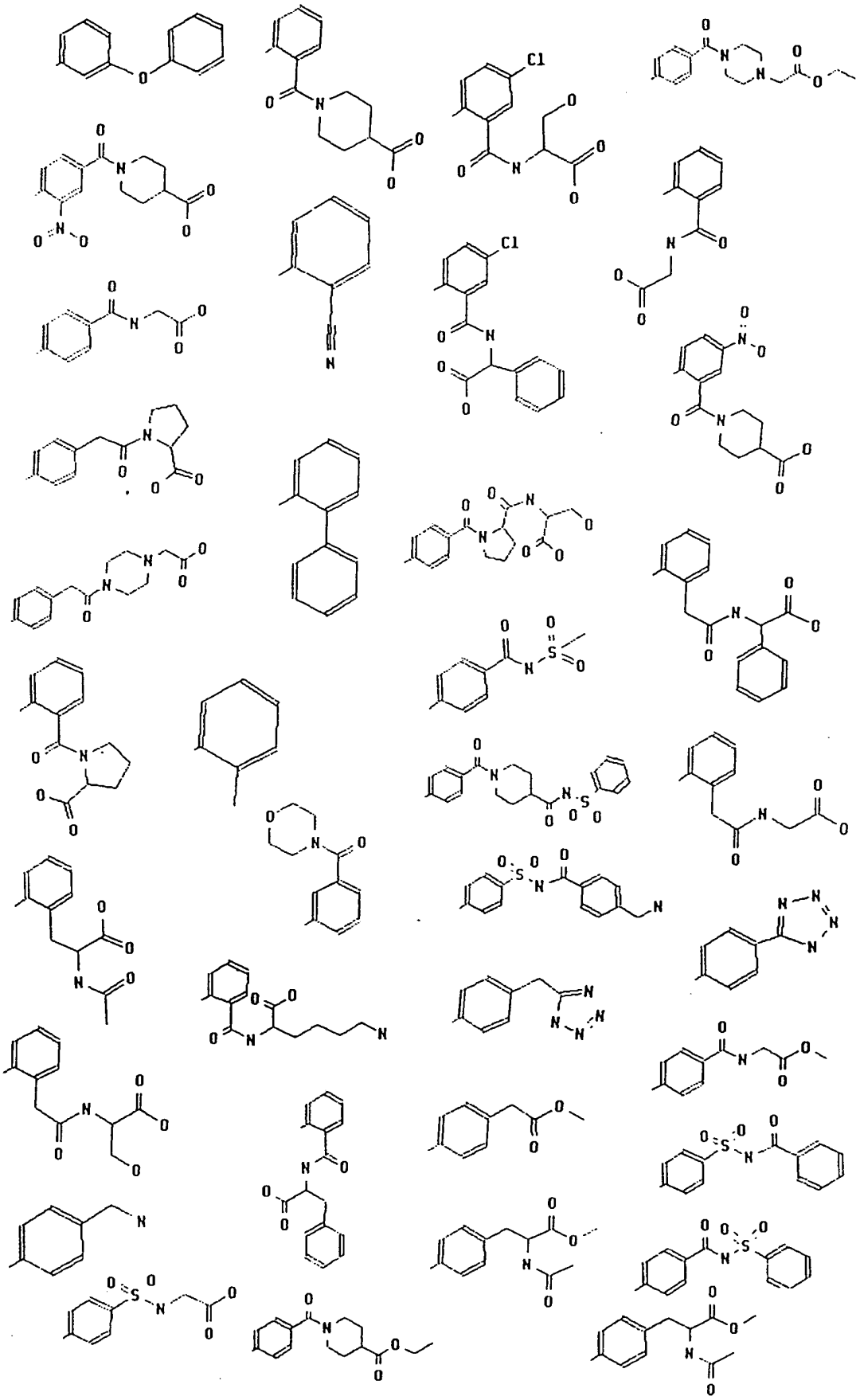
present on the para position.

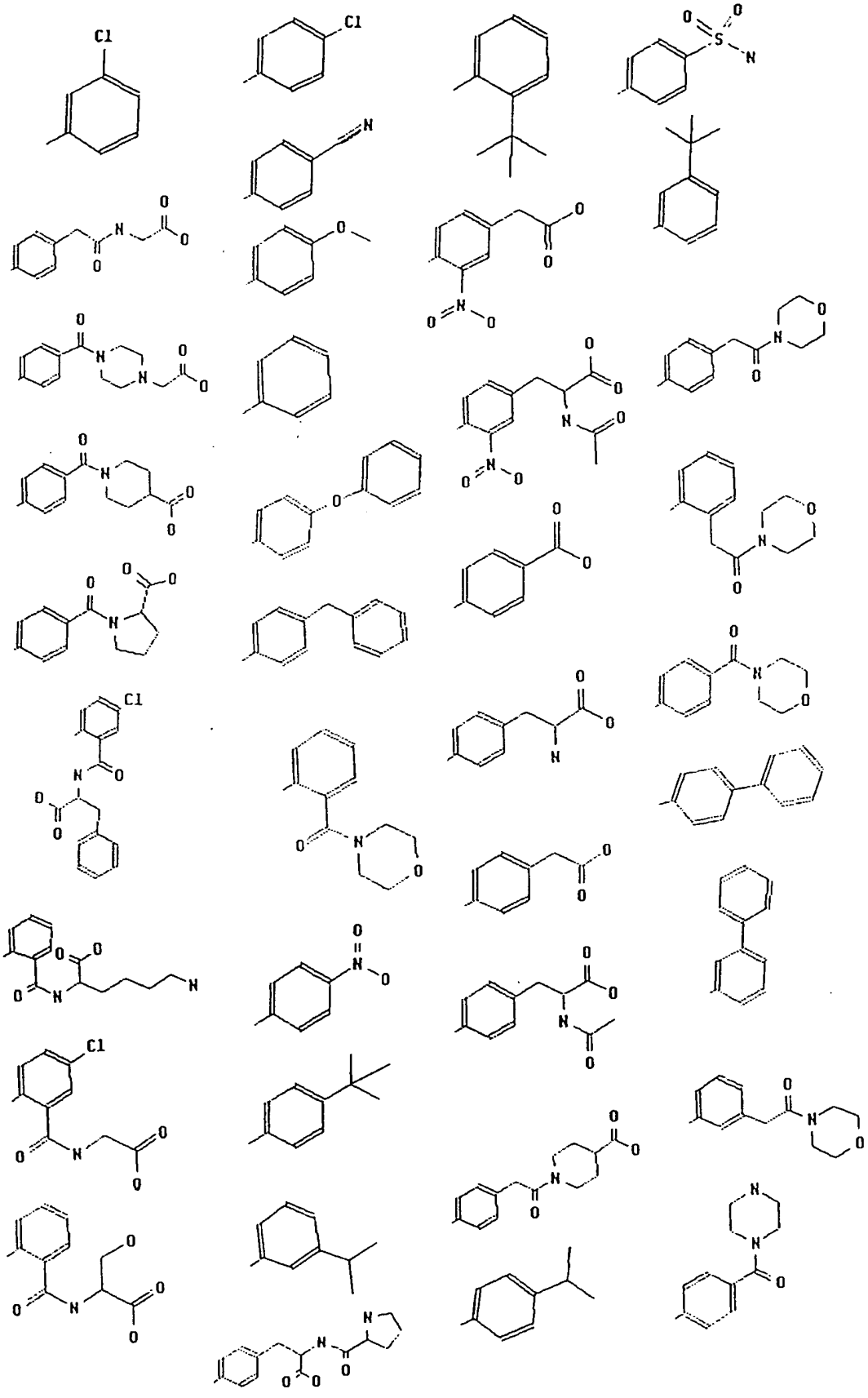
Where Ar represents a naphthyl derivative, the naphthyl may be substituted by one or more substituents selected from the same group as those as listed for phenyl above. Most preferred substituents are cyano, nitro, carboxamido, alkylaminosulfonyl, alkylsulfonyl, alkylsulfenyl, sulphonylaminoalkyl or trifluoromethyl or as for phenyl above naphthyl may be substituted by at least one polar moiety, most preferably an acidic or a protected form of an acidic moiety, such as alkyl or aryl carboxylic acids and esters, acyl sulphonamide, sulphonylamidocarboxyalkyl, carboxyamidosulphonylalkyl, tetrazole, sulphonic acid or phosphonic acid each bonded to the Ar ring directly or via an alkyl, sulphonamidoalkyl or carboxamidoalkyl linkage, the linkage itself being optionally substituted by small polar or apolar groups such as C_{1-4} alkyl, CN, NO_2, NH_2, NHCO-alkyl, or halogen.

Representative aromatic heterocyclic groups include pyridyl, quinolyl, isoquinolyl, imidazolyl, indolinyl, pyrazolinyl, pyrrolidinyl, imidazolidinyl, isoindolinyl, pyrazolidinyl, furyl, pyrolyl, pyrazinyl, benzothienyl, thienyl and benzofuryl. Particularly prefered heterocyclic groups are quinolyl, especially, 6-quinolyl and pyridyl, especially 3-pyridyl.

Optional substituents described above for one type of aryl Ar group may be present on the other types of aryl Ar groups. Suitable Ar groups therefore include (for convenience hydrogen atoms have been missed out):

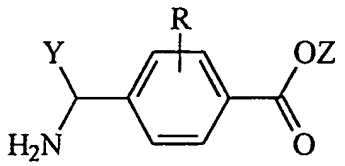






Where the compound of formula (I) is a salt, the salt is preferably a hydrochloride or other physiologically tolerated salt.

Viewed from another aspect the invention provides novel tryptase inhibitors of formula (II)



(II)

wherein R and Y are as hereinbefore defined; and

Z represents a phenyl group substituted by methylenedioxy, $-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w-Ph$, or R^1 and R^2 are optionally connected by a bond to form a 5-8 atom cyclic structure (eg. piperidine) or connected via an O, S or N atom to form a 5-8 atom heterocyclic structure (eg. morpholine, piperazine) and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; where R^3 is an oligomer comprising 1-4 aminoacid monomers, such as the natural aminoacids glycine, proline and serine, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2; or

Z represents a phenyl group subsituted in the 2-position by nitro or in the 3-position by methoxy; or

Z represents a naphthyl group substituted by halo,

for example fluoro, chloro, bromo or iodo, methylenedioxy, $-R^1$, $-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCO_2R^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w$-Ph, or R^1 and R^2 are optionally connected by a bond to form a 5-8 atom cyclic structure (eg. piperidine) or connected via an O, S or N atom to form a 5-8 atom heterocyclic structure (eg. morpholine, piperazine) and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; where R^3 is an oligomer comprising 1-4 aminoacid monomers, such as the natural aminoacids glycine, proline and serine, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2; or

a heterocyclic aryl groups containing 5 to 10 ring atoms including 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur; or

a physiologically tolerable salt thereof.

In a preferred embodiment, ZH should be less basic than benzylamine. This ensures that the compounds of the invention bind more efficiently in the tryptase active site.

In the compounds of formula (II), R is preferably a short chain alkyl, e.g. C_{1-3} alkyl such as methyl but most preferably R represents hydrogen. Y is preferably a short chain alkyl, e.g. C_{1-3} alkyl such as methyl but most preferably Y represents hydrogen and wherever possible Z represents a preferred substituent Ar as defined above.

Viewed from a further aspect the invention provides a tryptase inhibitor of formula (II) for use in combatting a condition responsive to said inhibitor.

Viewed from a yet further aspect the invention provides a pharmaceutical composition comprising a compound of formula (II), together with at least one pharmaceutically acceptable excipient.

The compounds of the invention may be prepared by conventional chemical synthetic routes, e.g. by ester bond formation to couple the Ar-OH compound to the aminomethylbenzoic acid derivative.

The readily available starting material 4-aminomethyl-benzoic acid can be utilised. Prior to esterification the amino group should be protected by any appropriate protecting group e.g. Boc, Z, Fmoc or Bpoc. The use of protecting groups is described in McOmie, "Protective Groups in Organic Chemistry", Plenum, 1973 and Greene, "Protective Groups in Organic Synthesis", Wiley Interscience, 1981. The protected aminomethyl-benzoic acid can be simply coupled to a suitable Ar-OH derivative by conventional esterification techniques before deprotection is effected.

If necessary the protected aminomethyl-benzoic acid derivative can be activated by converison to its corresponding anhydride or acyl chloride, using conventional reagents, to facilitate esterification. If the aminomethyl-benzoic acid compound is to carry phenyl substituents these can be conveniently introduced prior to the esterification or protection step using conventional aromatic substitution chemistry.

Alternatively, a starting material could be employed which already carries the substituent R and the aminomethyl functionality introduced for example by reduction of a cyano group. The Ar-OH alcohols are all readily available or prepared by the skilled chemist.

The compounds of the invention may be administered by any conventional route e.g. into the gastrointestinal

tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature or transdermally. However, it is prefered that the compounds be administered by inhalation, orally, intravenously or topically to the skin or to the eye. The compounds may be administered in any convenient administrative form e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents and further active agents. Preferably, the composition will be suitable for inhalation via a nebulizer or inhalable spray, e.g. a metered dose inhaler or dry powder inhaler for the treatment of lung conditions such as asthma. For dermatological or ophthalmic indications, the composition will be suitable for application to the skin or mucous membranes formulated as a cream, ointment or solution. Such compositions form a further aspect of the invention.

The dosage of the inhibitor compound of the invention will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However, in general, quantities to be administered are from 0.1 to 1000 mgs per day, preferably, 1 to 100 mgs per day. Conveniently, a suitable dosage, e.g 20mgs, can be admnistered by inhalation three times daily.

Thus, viewed from a further aspect the invention provides a method of treatment of human or non-human animal body (e.g. mammalian, avian or reptilian body) to combat a condition responsive to a tryptase inhibitor, said method comprising administering to said body an effective amount of a tryptase inhibitor according to the invention.

In a preferred embodiment the tryptase inhibitors of the invention can be administered along with other

active ingredients suitable for use in treating asthma, for example beta-adrenoceptor agonists such as salbutamol or anti-inflammatory agents such as cortiosteroids e.g. beclamethasone or cromolyns. It is envisaged that the tryptase inhibitors of the invention and the other active ingredient may act synergistically together. In a preferred embodiment the compounds of the invention are administered in conjunction with corticosteroids to reduce the dose of the steriod hence minimising steriod associated side effects.

Thus, viewed from a yet further aspect the invention provides a pharmaceutical composition comprising a compound of formula (I), together with one or more anti-asthma agents together with at least one pharmaceutically acceptable excipient.

It is envisaged that the compounds of the invention will be of use in combating mast cell mediated diseases such as asthma, allergic rhinitis, skin conditions such as eczema, atopic dermatitis and urticaria, rheumatoid arthritis, conjunctivitis and inflammatory bowel disease.

Although not wanting to be bound by any theory, it is expected that a tryptase inhibitor will be primarily administered chronically as prophylaxis to prevent or diminish exacerbations of the disease. However, for some diseases a more acute relief of symptoms may also be achievable.

For all the above conditions the compounds of the invention could be used alone or along side existing treatments and therapies.

The invention will now be described with reference to the following non-limiting examples.

Experimental

Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are Hplc, high-performance

liquid chromotography; MALDI-TOF, matrix assisted laser desorbtion ionisation - time of flight; rt, retention time; nmr, nuclear magnetic resonance. Alcohols and 4-aminomethylbenzoic acid were purchased from Aldrich (Gillingham, UK), Lancaster (Morecombe, UK), Avocado (Heysham, UK) or Ubichem.

Purification: Flash column chromotography[1] was carried out using Merck silica gel Si60 (40-63mm, 230-400 mesh).

Analysis: Proton nuclear magnetic resonance (^1H) spectra were recorded on Bruker DPX300 (300MHz). Analytical Hplc was on a Shimadzu LC6 gradient system equipped with an autosampler. Eluant A consisted of aqueous TFA (0.1%) and eluant B 90% MeCN in aqueous TFA (0.1%) with gradient elution (Gradient 1, 0min 20%B then 20%B to 100%B over 15min then 100%B for 5min; Gradient 2, 0min 20%B then 20%B to 100%B over 11 min; Gradient 3, 0min 50%B then 50%B to 100%B over 14min). Columns used were Jupiter 5 C18 column (2.1x150mm, 5μm particle size) and SymmetryShield RP_8 column (2.1x50mm, 3.5μm particle size). Purified products were further analysed by MALDI-TOF.

Example 1

Preparation of 2'-Naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

t-Butyloxycarbonylaminomethyl benzoic acid[2] (500mg, 2.0mmol) dissolved in dichloromethane (5ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (420mg, 2.2mmol). After stirring for 10 minutes 2-naphthol (316mg, 2.2mmol) and a catalytic ammount of N,N-dimethylaminopyridine were added. The resulting solution was stirred overnight at room temperature. After dilution with dichloromethane (20ml) the mixture was washed with saturated aqueous citric acid (25ml), saturated aqueous sodium bicarbonate (25ml)

water/acetonitrile/TFA) rt 10.88min.

Example 7

4'-Methoxyphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.26 (2H, d, J=8.3Hz, 2-H, 6-H); 7.66 (2H, d, J=8.3Hz, 3-H, 5-H); 7.16 (2H, d, J=9.1Hz, 2'-H, 6'-H); 7.00 (2H, d, J=9.1Hz, 3'-H, 5'-H); 4.25(2H, s, 4-CH_2); 3.83 (3H, s, OMe). M.S.TOF 258 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 11.84min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 9.00min.

Example 8

6'-Bromo-2'-naphthyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.15 (2H, d, J= 8.4Hz, 2-H, 6-H); 7.99 (1H, d, J=1.9Hz, 5'H); 7.78 (1H, d, J=9.0Hz, 4'-H); 7.67 (1H, d, J=8.8Hz, 8'-H); 7.61 (1H, d, J=2.2Hz, 1'-H); 7.52 (2H, d, J=8.4Hz, 3-H, 5-H); 7.48 (1H, dd, J=8.8, 1.9Hz, 7'-H); 7.29 (1H, dd, J= 9.0, 2.2Hz, 3'-H); 4.11 (2H, s, 4-CH_2). M.S. TOF 357 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 19.8 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.93 min.

Example 9

7'-Methoxy-2'-naphthyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.32 (2H, d, J=8.3Hz, 2-H, 6-H); 7.87 (1H, d, J=8.8Hz, 4'-H); 7.82 (1H, d, J=9.0Hz, 5'-H); 7.69 (2H, d, J=8.3Hz, 3-H, 5-H); 7.65 (1H, d, J=2.2Hz, 1'-H); 7.28 (1H, d, J=2.4Hz, 8'-H); 7.21 (1H, dd, J=8.8, 2.2Hz, 3'-H); 7.17 (1H, dd, J=9.0, 2.4, 6'-H); 4.28 (2H, s, 4-CH_2); 3.93 (3H, s, 7'-OMe). M.S. TOF 308 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 16.57 min. Hplc (SymmetryC8

and water (25ml), then dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purifed by flash column chromotography (10% - 30% ethyl acetate/hexane) to yield the 2'-naphthyl-4-(t-butyloxycarbonylaminomethyl)benzoate as a thick oil (620mg, 82% yield).
The deprotection was effected by dissolution in a mixture of trifluoroacetate (5ml) and dichloromethane (5ml). After stirring for 1 hour the mixture was concentrated under reduced pressure. Trituration with diethyl ether afforded 2'-naphthyl 4-(aminomethyl)benzoate trifluoracetic acid salt (580mg, 75% yield).

^{1}H nmr (d_4 methanol) 8.20 (2H, d, J=8.2Hz, 2-H, 6-H); 8.05-7.60 (3H, m, Ar); 7.58 (2H, d, J=8.2Hz, 3-H, 5-H); 7.45-7.20 (4H, m, Ar); 4.18 (2H, s, 4-CH_2). M.S.TOF 278 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.6 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.5 min.

Further examples were synthesised in an analagous manner using alcohols either commercially available or prepared using standard literature procedures. In several cases the deprotection step was effected using hydrogen chloride dissolved in diethyl ether to afford the products as hydrochloride salts.

Example 2

1'-Naphthyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.41 (2H, d, J=8.4Hz, 2-H, 6-H); 7.99 (1H, d, J=7.5Hz, Ar); 7.88 (2H, d, J=8.0Hz, Ar); 7.75 (2H, d, J=8.4Hz, 3-H, 5-H); 7.57 (3H, m, Ar); 7.40 (1H, m, Ar); 4.29 (2H, s, 4-CH_2). M.S.TOF 278 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.03min. Hplc (SymmetryC8, Gradient 2, water/acetonitrile/TFA) rt 10.43min.

Example 3

Phenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.27 (2H, d, J=8.3Hz, 2-H, 6-H); 7.68 (2H, d, J=8.3Hz, 3-H, 5-H); 7.52-7.20 (5H, m, Ph); 4.26 (2H, s, 4-CH_2). M.S.TOF 228 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 11.4 min. Hplc (Symmtry C8, Gradient 2, water/acetonitrile/TFA) rt 9.6 min.

Example 4

4'-Nitrophenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_6 DMSO) 8.58 (3H, bs, NH_3^+); 8.31-7.95 (4H, m, Ar); 7.85-7.30 (4H, m, Ar); 4.08 (2H, m, 4-CH_2). M.S.TOF 273 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 12.2 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 9.9 min.

Example 5

4'-Chlorophenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_6 DMSO) 8.59 (3H, bs, NH_3^+); 8.25 (2H, m, 2-H, 6-H); 7.80 (2H, m, 3'-H, 5'-H); 7.59 (2H, m, 3-H, 5-H); 7.40 (2H, m, 2'-H, 6'-H); 4.20 (2H, bs, 4-CH_2). M.S.TOF 262.5 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 14.8 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.2 min.

Example 6

1'-Bromo-2'-naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.27 (2H,d,J=8.4Hz, 2-H,6-H); 8.20 (1H, d, J=8.5Hz, Ar); 7.92 (2H, m, Ar); 7.61 (2H, d, J=8.4Hz, 3-H, 5-H); 7.54 (2H, m, Ar); 7.38 (1H, d, J=8.9Hz, Ar); 4.18 (2H, s, 4-CH_2). M.S.TOF 357 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 18.28min. Hplc (SymmetryC8, Gradient 2,

Gradient 2, Water/acetonitrile/TFA) rt 10.63 min.

Example 10

4'-Cyanophenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.29 (2H, d, J=8.3Hz, 2-H, 6-H); 7.87 (2H, d, J= 11.2Hz, 3'-H, 5'-H); 7.69 (2H, d, J=8.3Hz, 3-H, 5-H); 7.50 (2H, d, J=11.2Hz, 2'-H, 6'-H); 4.28 (2H, s, 4-CH_2); M.S. TOF 253 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 9.99 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 9.38 min.

Example 11

3'-Chlorophenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.27 (2H, d, J=8.3Hz, 2-H, 6-H); 7.67 (2H, d, J=8.3Hz, 3-H, 5-H); 7.50-7.44 (1H, dd, J=8.5, 8.2Hz, 5'-H); 7.38-7.33 (2H, m, Ar); 7.25-7.21 (1H, m, Ar); 4.27 (2H, s, 4-CH_2). M.S. TOF 263 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 14.71 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 11.29 min.

Example 12

6'-Methoxycarbonyl-2'-napthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.80 (1H, s, 5'-H); 8.45 (2H, d, J=8.3Hz, 2-H, 6-H); 8.23 (2H, m, 7'-H, 8'-H); 8.10 (1H, d, J=8.7Hz, 3'-H); 7.97 (1H, d, J=2.2Hz, 1'-H); 7.81 (2H, d, J=8.3Hz, 3-H, 5-H); 7.62 (1H, dd, J=8.7, 2.2Hz, 4'-H); 4.40 (2H, s, 4-CH_2); 4.18 (3H, s, 6'-CO_2Me). M.S.TOF 36 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.1 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.5 min.

Example 13

3'-Methoxycarbonyl-2'-naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.70 (1H, s, 1'-H); 8.31 (2H, d, J=8.4Hz, 2-H, 6-H); 8.09 (1H, d, J=8.2Hz, 8'-H); 7.97 (1H, d, J=7.9Hz, 5'-H); 7.78 (1H, s, 4'-H); 7.76-7.60 (4H, m, Ar); 4.28 (2H, s, 4-CH_2); 3.80 (3H, s, 3'-CO_2Me). M.S.TOF 336 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.4 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.4 min.

Example 14

1'-Methoxycarbonyl-2'-naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.08 (2H, d, J=7.9Hz, 2-H, 6-H); 8.02 (1H, d, J=9.0Hz, 3'-H); 7.95- 7.85 (2H, m, 5'-H, 8'-H); 7.60 (2H, d, J=7.9Hz, 3-H, 5-H); 7.50 (2H, m, 6'-H, 7'-H); 7.38 (1H, d, J=9.0Hz, 4'-H); 4.25 (2H, s, 4-CH_2); 3.78 (3H, s, 1'-CO_2Me). M.S.TOF 336 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.6 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.4 min.

Example 15

5',6',7',8'-Tetrahydro-2-naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.13 (2H, d, J=8.4Hz, 2-H, 6-H); 7.54 (2H, d, J=8.4Hz, 3-H, 5-H); 7.01 (1H, d, J=9.0Hz, Ar); 6.81 (2H, m, Ar); 4.12 (2H, s, 4-CH_2); 2.70 (4H, m, 5'-H, 8'-H); 1.73 (4H, m, 6'-H, 7'-H). M.S.TOF 282 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 17.84min. Hplc (SymmetryC8, Gradient 2, water/acetonitrile/TFA) rt 10.75min.

Example 16

6'-Quinolinyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 9.46 (2H, m, Ar); 8.61 (1H, d,

J=9.3Hz, Ar); 8.54 (3H, m, Ar); 8.37 (2H, m, Ar); 7.93 (2H, d, J=8.3Hz, 3-H, 5-H); 4.48 (2H, s, 4-CH_2). M.S.TOF 279 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 7.07min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 3.44min.

Example 17

3'-iso-Propylphenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.16 (2H, d, J=8.4Hz, 2-H, 6-H); 7.57 (2H, d, J=8.4Hz, 3-H, 5-H); 7.27 (1H, t, J=7.8Hz, 5'-H); 7.09 (1H, d, J=7.8Hz, 6'-H); 7.00 (1H, m, 2'-H); 6.93 (1H, m, 4'-H); 4.17 (2H, s, 4-CH_2); 2.88 (1H, sep, J=6.9Hz, 3'-CH); 1.08 (6H, d, J=6.9Hz, 3'-CMe_2). M.S.TOF 270 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 17.6 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.6 min.

Example 18

4'-Biphenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.18 (2H, d, J=8.3Hz, 2-H, 6-H); 7.61 (2H, d, J=8.3Hz, 3-H, 5-H); 7.57-7.17 (9H, m, Ar); 4.18 (2H, s, 4-CH_2). M.S.TOF 304 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 18.9 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.8 min.

Example 19

4'-(t-Butyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.15 (2H, d, J=8.4Hz, 2-H, 6-H); 7.55 (2H, d, J=8.4Hz, 3-H, 5-H); 7.38 (2H, d, J=8.8Hz, 2'-H, 6'-H); 7.08 (2H, d, J=8.8Hz, 3'-H, 5'-H); 4.18 (2H, s, 4-CH_2); 1.26 (9H, s, 4'-^{t}Bu). M.S.TOF 284 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 19.5 min. Hplc (Symmetry C8, Gradient 2,

water/acetonitrile/TFA) rt 10.9 min.

Example 20

7'-Hydroxy-2'-naphthyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.32 (2H, d, J=8.3Hz, 2-H, 6-H); 7.84 (1H, d, J= 8.9Hz, 4'-H); 7.78 (1H, d, J=8.7Hz, 5'-H); 7.69 (2H, d, J=8.3Hz, 3-H, 5-H); 7.51 (1H, d, J=2.2Hz, 1'-H); 7.18-7.08 (3H, m, 3'-H, 6'-H, 8'-H); 4.28 (2H, s, 4-CH_2). M.S. TOF 294 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 12.75 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.00 min.

Example 21

4'-iso-Propylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.26 (2H, d, J=8.4Hz, 2-H, 6-H); 7.67 (2H, d, J=8.4Hz, 3-H, 5-H); 7.34 (2H, d, J=8.6Hz, 2'-H, 6'-H); 7.15 (2H, d, J=8.6Hz, 3'-H, 5'-H); 4.26 (2H, s, 4-CH_2); 2.98 (1H, sep, J= 6.8Hz, 4'-CH); 1.30 (6H, d, J=6.8Hz, 4'-CMe_2). M.S. TOF 270 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 18.27 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.70 min.

Example 22

4'-Benzylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.38 (2H, d, J=8.3Hz, 2-H, 6-H); 7.78 (2H, d, J=8.3Hz, 3-H, 5-H); 7.45-7.25 (9H, m, Ar); 4.38 (2H, s, 4-CH_2); 4.15 (2H, s, 4'-CH_2). M.S. TOF 318 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 19.80 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.96 min.

Example 23

3'-Methoxyphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.11 (2H, d, J=8.3 Hz, 2-H, 6-H); 7.51 (2H, d, J=8.3 Hz, 3-H, 5-H); 7.24-7.18 (1H, m, 5'-H); 6.76-6.65 (3H, m, 2'-H, 4'-H, 6'-H); 4.11 (2H, s, 4-CH_2); 3.68 (3H, s, 3'-OMe). M.S. TOF 258 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 12.56 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 9.69 min.

Example 24

8'-Methoxycarbonyl-2'-naphthyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.88 (1H, d, J=9.4Hz, 4'-H); 8.19 (2H, d, J=8.4Hz, 2-H, 6-H); 8.10 (1H, d, J=8.3Hz, Ar); 8.10 (1H, dd, J=7.3, 1.1Hz, Ar); 8.02 (1H, d, J=8.3Hz, Ar); 7.72 (1H, d, J=2.4Hz, 1'-H); 7.57 (2H, d, J=8.4Hz, 3-H, 5-H); 7.49 (1H, m, Ar); 7.42 (1H, dd, J=9.4, 2,4Hz, 3'-H); 4.18 (2H, s, 4-CH_2); 3.90 (3H, s, 5'-CO_2Me). M.S.TOF 336 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.6 min. Hplc (Symmetry C8, Gradient 2, water/acetonitrile/TFA) rt 10.5 min.

Example 25

1'-Amino-2'-naphthyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_6 DMSO) 8.59 (3H, bs, 1'-NH); 8.47 (1H, d, J=8.1Hz, Ar); 8.32 (2H, d, J=8.2Hz, 2-H, 6-H); 8.15 (1H, d, J=8.2Hz, Ar); 8.01 (2H, s, Ar); 7.77 (3H, d, J=8.2Hz, Ar); 7.64 (1H, t, J=7.1Hz, Ar); 4.15 (2H, s, 4-CH_2). M.S.TOF 294 $(M+2)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 15.57min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 8.65min

Example 26

7'-Quinolinyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 9.15 (1H, d, J=4.1Hz, Ar); 8.98 (1H, d, J=8.2Hz, Ar); 8.36 (3H, d, J=8.3Hz, Ar); 8.18 (1H, d, J=1.5Hz, Ar); 7.94 (1H, dd, J=8.3, 5.0Hz, Ar); 7.85 (1H, m); 7.74 (2H, d, J=8.2Hz, 3-H, 5-H); 4.29 (2H, s, 4-CH_2). M.S.TOF 282 $(M+2)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 2.15min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 4.76min.

Example 27

3'-(t-Butyl)phenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.17 (2H, d, J=8.3Hz, 2-H, 6-H); 7.56 (2H, d, J=8.3Hz, 3-H, 5-H,); 7.27 (2H, m, Ar); 7.14 (1H, m, Ar); 6.93 (1H, m, Ar); 4.16 (2H, s, 4-CH_2); 1.24 (9H, s, 3'-^{t}Bu). M.S.TOF 284 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 18.78min. Hplc (SymmetryC8, Gradient 2, water/acetonitrile/TFA) rt 10.85min.

Example 28

3'-Biphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.31 (2H, d, J=8.4Hz, 2-H, 6-H); 8.12 (2H, d, J=7.8Hz, Ar); 7.74-7.23 (7H, m, Ar); 7.01 (2H, d, J=7.7Hz, Ar); 4.28 (2H, s, 4-CH_2). M.S.TOF 304 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 18.57min. Hplc (SymmetryC8, Gradient 2, water/acetonitrile/TFA) rt 10.90min.

Example 29

4'-Phenoxyphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 7.93 (2H, d, J=8.3Hz, 2-H, 6-H); 7.58 (2H, d, J=9.0Hz, Ar); 7.51 (2H, d, J=8.3Hz, 3-H, 5-H); 7.25 (2H, m, Ar); 7.01 (1H, m, Ar); 6.91 (4H, m, Ar); 4.11 (2H, s, 4-CH_2). M.S.TOF 320 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.55min. Hplc (SymmetryC8, Gradient 2,

water/acetonitrile/TFA) rt 10.55min.

Example 30

3'-Phenoxyphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 7.90 (2H, d, J=8.2Hz, 2-H, 6-H); 7.50 (2H, d, J=8.2Hz, 3-H, 5-H); 7.4-7.2 (5H, m, Ar); 7.03 (1H, t, J=7.4Hz, Ar); 6.93 (2H, d, J=7.7Hz, Ar); 6.68 (1H, m, Ar); 4.11 (2H, s, 4-CH_2). M.S.TOF 320 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 16.82min. Hplc (SymmetryC8, Gradient 2, water/acetonitrile/TFA) rt 10.48min.

Example 31

5'-Amino-2'-naphthyl 4-(aminomethyl)benzoate ditrifluoracetic acid salt

^{1}H nmr (d_4 methanol) 8.21 (2H, d, J=8.3Hz, 2-H, 6-H); 7.98 (1H, d, J=9.2Hz, Ar); 7.71 (1H, d, J=2.3Hz, 1'-H); 7.63 (1H, d, J=8.4Hz, Ar); 7.58 (2H, d, J=8.3Hz, 3-H, 5-H); 7.40 (2H, m, Ar); 7.21 (1H, m, Ar); 4.15 (2H, s, 4-CH_2). M.S.TOF 293 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 4.3min. Hplc (Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 7.5 min.

Example 32

8'-Amino-2'-naphthyl 4-(aminomethyl)benzoate ditrifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.20 (2H, d, J=8.4Hz, 2-H, 6-H); 7.82 (1H, d, J=9.0Hz, Ar); 7.78 (1H, d, J=2.2Hz, 1'-H); 7.58 (2H, d, J=8.4Hz, 3-H, 5-H); 7.42 (1H, d, J=8.3Hz, Ar); 7.27 (2H, m, Ar); 6.98 (1H, m, Ar); 4.15 (2H, s, 4-CH_2). M.S.TOF 292 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 8.4 min. Hplc (Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 7.4 min.

Example 33

5'-Quinolinyl 4-(aminomethyl)benzoate ditrifluoroacetate

salt

^{1}H nmr (d_4 methanol) 8.97 (1H, d, J=4.3Hz, Ar); 8.59 (1H, d, J=8.5Hz, Ar); 8.30 (2H, d, J=8.1Hz, 2-H, 6-H); 8.01 (1H, d, J=8.6Hz, Ar); 7.91 (1H, t, J=8.1Hz, Ar); 7.70-7.60 (2H, m, Ar); 7.63 (2H, d, J=8.1Hz, 3-H, 5-H); 4.20 (2H, s, 4-CH_2). M.S. TOF 279 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt 9.83 min.

Example 34

8'-Quinolinyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 9.12 (1H, dd, J=1.4, 8.4Hz, Ar); 9.06 (1H, dd, J=1.4, 5.2Hz, Ar); 8.33 (2H, d, J=8.4Hz, 2-H, 6-H); 8.19 (1H, dd, J=1.7, 7.9Hz, Ar); 8.03-7.92 (3H, m, Ar); 7.65 (2H, d, J=8.4Hz, 3-H, 5-H); 4.21 (2H, s, 4-CH_2). M.S. TOF 279 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt 11.95 min.

Example 35

5'-Isoquinolinyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 9.84 (1H, s, 1'-H); 8.69 (1H, d, J=6.6Hz, Ar); 8.58 (2H, m, Ar); 8.47 (2H, d, 8.4Hz, 2-H, 6-H); 8.29 (1H, dd, J=6.7, 7.8Hz, Ar); 8.20 (1H, d, J=7.9Hz, 4'-H); 7.81 (2H, d, J=8.4Hz, 2-H, 5-H); 4.21 (2H, s, 4-CH_2). M.S. TOF 279 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt 9.79 min.

Example 36

4'-Quinolinyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 9.22 (1H, d, J=6.4Hz, 2'-H); 8.50 (1H, d, J=8.4Hz, Ar); 8.37 (2H, d, J=8.3Hz, 2-H, 6-H); 8.25 (1H, d, J=6.3Hz, 3'-H); 8.22-8.17 (2H, m, Ar); 8.00-7.94 (1H, m, Ar); 7.70 (2H, d, J=8.3Hz, 3-H, 5-H), 4.23 (2H, s, 4-CH_2). M.S. TOF 279 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt 9.45 min.

Example 37

3'-Pyridyl 4-(aminomethyl)benzoate dihydrochloride salt

^{1}H nmr (d_4 methanol) 8.98 (1H, d, J=2.2Hz, 2'-H); 8.72 (1H, d, J=5.4Hz, 4'-H); 8.53-8.49 (1H, m, 6'-H); 8.25 (2H, d, J=8.5Hz, 2-H, 6-H); 8.07 (1H, dd, J=5.6, 8.7Hz, 5'-H); 7.62 (2H, d, J=8.5Hz, 3-H, 5-H); 4.18 (2H, s, 4-CH_2). M.S. TOF 229 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt 7.26 min.

Example 38

3'-(N-Morpholino)carbonylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.17 (2H, d, J=8.2Hz, 2-H, 6-H); 7.58 (2H, d, J=8.2Hz, 3-H, 5-H); 7.48 (1H, m, Ar); 7.30 (1H, d, J=1.5Hz, Ar); 7.27 (2H, s, Ar); 4.13(2H, s, 4-CH_2); 3.7-3.3 (8H, m, 3'-$N(CH_2CH_2)_2$). M.S.TOF 341 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 4.97min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 7.66min.

Example 39

4'-(N-Morpholino)carbonylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.05 (2H, d, J=8.3Hz, 2-H, 6-H); 7.49 (2H, d, J=8.3Hz, 3-H, 5-H); 7.36 (2H, d, J=8.5Hz, 3'-H, 5'-H); 7.17 (2H, d, J=8.5Hz, 2'-H, 6'-H); 4.06 (2H, s, 4-CH_2); 3.6-3.2 (8H, m, 4'-$N(CH_2CH_2)_2$). M.S.TOF 341 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 3.77min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 7.69min.

Example 40

2'-(N-Morpholino)carbonylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.06 (2H, d, J=8.3Hz, 2-H, 6-H); 7.50 (2H, d, J=8.3 Hz, 3-H, 5-H); 7.41 (1H, m, Ar); 7.25 (3H, m, Ar); 4.07 (2H, s, 4-CH_2); 3.6-3.1 (8H, m, 2'-

$N(CH_2CH_2)_2$). M.S.TOF 341 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 5.66min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 7.80min.

Example 41

3'-((N-Morpholino)carbonylmethyl)phenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.50 (2H, d, J=8.3Hz, 2-H, 6-H); 7.92 (2H, d, J=8.3Hz, 3-H, 5-H); 7.67 (1H, m, Ar); 7.48 (1H, d, J=7.6Hz, Ar); 7.40 (2H, d, J=8.0Hz, Ar); 4.50 (2H, s, 3'-CH_2); 4.09 (2H, s, 4-CH_2); 3.9-3.7 (8H, m, 3'-$N(CH_2CH_2)_2$). M.S.TOF 355 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 6.54min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 7.76min.

Example 42

4'-((N-Morpholino)carbonylmethyl)phenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.15 (2H, d, J=8.3Hz, 2-H, 6-H); 7.55 (2H, d, J=8.3Hz, 3-H, 5-H); 7.26 (2H, d, J=8.6Hz, Ar); 7.11 (2H, d, J=8.6Hz, Ar); 4.14 (2H, s, 4-CH_2); 3.71 (2H, s, 4'-CH_2); 3.7-3.3 (8H, m, 4'-$N(CH_2CH_2)_2$). M.S.TOF 355 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 5.93min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 7.71min.

Example 43

2'-((N-Morpholino)carbonylmethyl)phenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.21 (2H, s, Ar); 7.67 (2H, s, Ar); 7.35 (2H, m, Ar); 7.26 (2H, m, Ar); 4.21 (2H, s, 4-CH_2); 3.75 (2H, s, 2'-CH_2); 3.6-3.3 (8H, m, 2'-$N(CH_2CH_2)_2$). M.S.TOF 355 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, water/acetonitrile/TFA) rt 5.68min. Hplc (SymmetryC8, Gradient 5, water/acetonitrile/TFA) rt 8.58min.

Example 44

2'-Biphenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.08 (2H, d, J=8.3Hz, 2-H, 6-H); 7.57 (2H, d, J=8.3Hz, 3-H, 5-H); 7.51-7.39 (5H, m, Ar); 7.33-7.21 (4H, m, Ar); 4.21 (2H, s, 4-CH_2); M.S. TOF 304 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 16.04 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.54 min.

Example 45

2'-(t-Butyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.30 (2H, d, J=8.4Hz, 2-H, 6-H); 7.70 (2H, d, J=8.4Hz, 3-H, 5-H); 7.53-7.48 (1H, m, 6'-H); 7.33- 7.21 (2H, m, 5'-H, 4'-H); 7.05-7.11 (1H, m, 3'-H); 4.28 (2H, s, 4-CH_2); 1.38 (9H, s, 2'-^{t}Bu); M.S. TOF 284 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/ TFA) rt 16.64 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 10.69 min.

Example 46

4'-(2-Phenylethenyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.16 (2H, d, J=8.3Hz, 2-H, 6-H); 7.57-7.07 (13H, m, Ar, CH=CH); 4.15 (2H, s, 4-CH_2). M.S. TOF 330 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 8, Water/acetonitrile/TFA) rt 13.47 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 11.31 min.

Example 47

4'-(2-Phenylethyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.14 (2H, d, J=8.3Hz, 2-H, 6-H); 7.57 (2H, d, J=8.3Hz, 3-H, 5-H); 7.18-6.97 (9H, m, Ar); 4.15 (2H, s, 4-CH_2); 2.84 (4H, s, 4'-CH_2CH_2). M.S. TOF

332 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 8, Water/acetonitrile/TFA) rt 13.47 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 11.25 min.

Example 48

2'-Nitrophenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.16 (2H, d, J=8.1, 2-H, 6-H); 8.09 (1H, dd, J=1.0, 8.1Hz, 3'-H); 7.73 (1H, t, J=7.2Hz, 5'-H); 7.59 (2H, d, J=8.1Hz, 3-H, 5-H); 7.46 (1H, t, J=7.8Hz, 4'-H); 7.41 (1H, d, J=8.0Hz, 6'-H); 4.17 (2H, s, 4-CH_2). M.S. TOF 273 $(M+1)^+$. HPLC (Jupiter5 C18, water/acetonitrile/TFA, gradient 2) rt

Example 49

2'-Cyanophenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.21 (2H, d, J=8.4Hz, 2-H, 6-H); 7.77-7.67 (2H, m, Ar); 7.59 (2H, d, J=8.4Hz, 3H, 5H); 7.46-7.36 (2H, m, Ar); 4.17 (2H, s, 4-CH_2). M.S. TOF 253 $(M+1)^+$.

Example 50

2'-Methylphenyl 4-(aminomethyl)benzoate hydrochloride salt

^1H nmr (d_4 methanol) 8.17 (2H, d, J=8.2Hz, 2-H, 6-H); 7.59 (2H, d, J=8.2Hz, 3-H, 5-H); 7.23-7.01 (4H, m, Ar); 4.16 (2H, s, 4-CH_2). M.S. TOF 242 $(M+1)^+$

The following examples were prepared in a similar manner. Suitably protected alcohols were bought or synthesised by conventional means and aminomethylbenzoic acid was purchased and used as previously described.

Analysis: Proton nuclear magnetic resonance (^1H) spectra were recorded on Bruker DPX300 (300MHz). Analytical Hplc was on a Shimadzu LC6 gradient system equipped with an

autosampler. Eluant A consisted of aqueous TFA (0.1%) and eluant B 90% MeCN in aqueous TFA (0.1%) with gradient elution (Gradient 4, 0min 20%B then 20%B to 53.3%B over 15min the 53.3%B for 1min then 100%B for 1min; Gradient 5, 0min 20%B then 20%B to 100%B over 15min then 100%B for 5min; Gradient 6, 0min 20%B then 20%B to 100%B over 5 min then 100%B for 1min). Columns used were Magellan C8 column (2.1 x 150mm, 5μm particle size) and Magellan C18 column (4.6 x 30mm, 3μm particle size). Purified products were further analysed by LC-MS (PESCIEX Single Quadropole API-150EX).

Example 51

4-(Methoxycarbonylmethyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.25 (2H, d); 7.65 (2H, d); 7.38 (2H, d); 7.20 (2H, d); 4.29 (2H, s);3.72 (5H,s) M.S.TOF 300 $(M+1)^+$, Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 12.06min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.27min, 300 $(M+1)^+$.

Example 52

4-[(2-Acetylamino-2-carboxy)ethyl]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.00 (2H, d); 7.43 (2H, d); 6.98 (2H, d); 4.48 (1H, m); 4.0 (2H, s); 3.01 (1H, dd); 2.78 (1H, dd); 1.72 (3H, s). Hplc (magellan C8, Gradient 5, water/acetonitrile/TFA) rt 9.4min. LC-MS (magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.69min, 357 $(M+1)^+$.

Example 53

4-[(N-Carboxymethyl)carboxamido]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.31 (2H, d); 8.02 (2H, d); 7.71 (2H, d); 7.42 (2H, d); 4.29 (2H, s); 4.16 (2H, s). Hplc

(Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 7.23 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.45 min, 329 $(M+1)^+$.

Example 54

4-(Carboxymethyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.27 (2H, d); 7.68 (2H, d); 7.39 (2H, d); 7.20 (2H, d); 4.24 (2H, s);3.69 (2H,s), Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 9.94min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt1.80min, 286 $(M+1)^+$.

Example 55

O-[Methyl N-acetyl-L_tyrosinyl] 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.22 (2H, d); 7.63 (2H, d); 7.31 (2H, d); 7.20 (2H, d); 4.72 (1H, m); 4.27 (2H, s); 3.69 (3H, s); 3.21 (3H, s); 3.21 (1H, dd); 3.01 (1H, dd); 2.92 (3H, s). Hplc (magellan C8, gradient 5, water/acetonitrile/TFA) rt 8.3min. LC-MS (magellan C18, Gradient 5, water/acetonitrile/TFA) rt 1.98 min, 371 $(M+1)^+$.

Example 56

4-[N-[(Methoxycarbonyl)methyl]carboxamido]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.30 (2H, d); 7.95 (2H, d); 7.32 (2H, d); 4.28 (2H, s); 4.12 (2H, s); 3.71 (3H, s). Hplc (magellan C8, Gradient 5, water/acetonitrile/TFA) rt 9.10min. LC-MS (magellan C18, Gradient 5, water/acetonitrile/TFA) rt 1.65min, 343 $(M+1)^+$.

Example 57

4-[4-Carboxypiperidin-1-oyl]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.10 (2H, d); 7.39 (2H, d); 7.32

(2H, d); 7.18 (2H, d); 4.32 (1H, m); 4.12 (2H, s); 3.65 (1H, m); 3.05 (2H, m); 2.60 (1H, m); 2.82 (2H, m); 1.50 (2H, m). Hplc (magellan C8, Gradient 5, water/acetonitrile/TFA) rt 8.4min. LC-MS (magellan C18, Gradient 5, water/acetonitrile/TFA) rt 1.69min, 383 $(M+1)^+$.

Example 58

4-(2-Carboxypyrrolidin-1-oyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.15 (2H, d); 7.58 (4H, m); 7.29 (2H, d); 4.53 (1H, m); 4.15 (2H, s);3.70-3.50 (2H, m); 2.30 (1H, m); 2.10-1.80 (3H, m), Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 9.34min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.73min, 369 $(M+1)^+$.

Example 59

4-[4-(Ethoxycarbonyl)piperidin-1-oyl]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.27 (2H, d); 7.62 (2H, d); 7.52 (2H, d); 7.39 (2H, d); 4.48 (1H, s); 4.29 (2H, s); 4.15 (2H, ; 3.77 (1H, m); 3.22 (2H, m); 2.73 (1H, m); 2.05 (2H, m); 1.70 (2H, m); 1.30 (3H, t). Hplc (magellan C8, Gradient 5, water/acetonitrile/TFA) rt 7.29 min. LC-MS (magellan C18, Gradient 5, water/acetonitrile/TFA) rt 2.41min, 411 $(M+1)^+$.

Example 60

3-(4-Carboxypiperidin-1-oyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.32 (2H, d); 7.69 (2H, d); 7.62 (1H, t); 7.43-7.36 (3H, m); 4.56-4.45 (1H, m); 4.29 (2H, s); 3.86-3.74 (1H, m), 3.36-3.09 (2H, m); 2.75-2.64 (1H, m); 2.16-1.89 (2H, m); 1.82-1.96 (2H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.03 min. LC-MS (Magellan C18, Gradient 6,

water/acetonitrile/TFA) rt 1.68 min, 383 $(M+1)^+$.

Example 61

2-(4-Carboxypiperidin-1-oyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.23 (2H, d); 7.67 (2H, d); 7.62 (1H, m); 7.48-7.37 (3H, m); 4.45-4.30 (1H, m); 4.26 (2H, s); 3.67-3.57 (1H, m), 3.25-3.08 (1H, m); 2.99-2.87 (1H, m); 2.62-2.51 (1H, m); 1.95-1.81 (2H, m); 1.72-1.26 (2H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.03 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.80 min, 383 $(M+1)^+$.

Example 62

4-[2-(N-(1-Carboxy-2-hydroxy)ethyl)carboxamido-pyrrolidin-1-oyl]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.15 (2H, d); 7.64 (2H, d); 7.57 (2H, d); 7.24(2H, d); 4.60 (1H, m); 4.48 (1H, m); 4.17 (2H, s);3.90-3.20 (4H, m); 2.28 (1H, m); 2.10-1.60 (3H, m), Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 8.17min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.35min, 456 $(M+1)^+$.

Example 63

4-[(4-Ethoxycarbonylmethyl)piperazin-1-oylphenyl] 4-(aminomethyl)benzoate triflouroacetate salt

^1H nmr (d_4 methanol) 8.31 (2H, d); 7.83 (2H, d); 7.79 (2H, d); 7.57 (2H, d); 4.50 (2H, q); 4.42 (2H, s); 4.30 (2H, s); 4.10 (4H, bs); 3.58 (4H, bs); 1.50 (3H, t). Hplc (magellan C8, Gradient 5, water/acetonitrile/TFA) rt 7.37min. LC-MS (magellan C18, Gradient 5, water/acetonitrile/TFA) rt 1.40min, 426 $(M+1)^+$.

Example 64

4-[4-(Phenylsulfonylcarboxamido)piperidin-1-oyl]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.30 (2H, d); 8.05 (2H, d); 7.76-7.60 (5H, m); 7.54 (2H, d); 7.39 (2H, d), 4.60-4.49 (1H, m); 4.29 (2H, s); 3.87-3.74 (1H, m), 3.26-2.95 (2H, m); 2.64-2.53 (1H, m); 1.95-1.70 (2H, m); 1.68-1.53 (2H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.17 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.29 min, 522 $(M+1)^+$.

Example 65

4-Carboxyphenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.28 (2H, d); 8.14 (2H, d); 7.69 (2H, d); 7.38 (2H, d); 4.27 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 7.81 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.27 min, 272 $(M+1)^+$.

Example 66

2-(2-Carboxypyrrolidin-1-oyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.25 (2H, d); 7.70-7.30 (6H, m); 4.40 (1H, m); 4.25 (2H, s); 3.50 (2H, m); 2.40-1.80 (4H, m), Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 8.76min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.83min, 369 $(M+1)^+$.

Example 67

3-(2-Carboxypyrrolidin-1-oyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.40 (2H, d); 7.80(2H, d); 7.70-7.40 (4H, m); 4.80-4.50 (1H, m); 4.39 (2H, s); 3.80 (2H, m); 2.50 (1H, m); 2.15 (3H, m), Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 7.68min, LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.93min, 369

$(M+1)^+$.

Example 68

4-(N-Phenylsulfonylcarboxamido)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.27 (2H, d); 8.12 (2H, d); 8.00 (2H, d); 7.71-7.58 (5H, m); 7.37 (2H, d); 4.29 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.74 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.61 min, 411 $(M+1)^+$.

Example 69

4-(Tetrazolylmethyl)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.27 (2H, d); 7.68 (2H, d); 7.49 (2H, d); 7.30 (2H, d); 4.27 (2H, s);3.97 (2H,s) M.S.TOF 310 $(M+1)^+$, Hplc (Magellan C8, Gradient 4, water/acetonitrile/TFA) rt 10.15min, Hplc (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.12min.

Example 70

4-(N-Methanesulfonylcarboxamido)phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.25 (2H, d); 8.01 (2H, d); 7.68 (2H, d); 7.43 (2H, d); 4.28 (2H, s); 3.39 (3H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 7.68 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.74 min, 349 $(M+1)^+$.

Example 71

4-[(2-Amino-2-carboxy)ethyl]phenyl 4-(aminomethyl)benzoate ditrifluoroacetate salt

^1H nmr (d_4 methanol) 8.28 (2H, d); 7.70 (2H, d); 7.46 (2H, d); 7.29 (2H, d); 4.29 (2H, s); 4.19 (1H, dd); 3.41 (1H, dd); 3.20 (1H, dd). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 6.77 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.35 min,

315 $(M+1)^+$.

Example 72

[4-(4-Carboxypiperidin-1-oyl)-2-nitro]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.33-8.28 (3H, m); 7.91 (1H, dd); 7.73 (2H, d); 7.66 (1H, d); 4.57-4.38 (1H, m); 4.31 (2H, s); 3.83-3.70 (1H, m), 3.36-3.13 (2H, m); 2.78-2.66 (1H, m); 2.17-1.92 (2H, m); 1.87-1.69 (2H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.49 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 1.83 min, 428 $(M+1)^+$.

Example 73

[2-(4-Carboxypiperidin-1-oyl)-4-nitro]phenyl 4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.48 (1H, dd); 8.39 (1H, br s); 8.26 (2H, d); 7.77-7.67 (3H, m); 4.51-4.36 (1H, m); 4.30 (2H, s); 3.68-3.59 (1H, m), 3.31-3.18 (1H, m); 3.02 (1H, td); 2.68-2.58 (1H, m); 2.00-1.90 (2H, m); 1.78-1.30 (2H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.18 min. LC-MS (Magellan C18, Gradient 6, water/acetonitrile/TFA) rt 2.07 min, 428 $(M+1)^+$.

Example 74

4-Sulphonamidophenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.28 (2H, d); 8.02 (2H, d); 7.68 (2H, d); 7.46 (2H, d); 4.27 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.70 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.17 min, 307 $(M+1)^+$.

Example 75

(4-Carboxymethyl-2-nitro)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) ^1H nmr (d_4 methanol) 8.29 (2H, d);

8.18 (1H, d); 7.78 (1H, dd); 7.71 (2H, d); 7.49 (1H, d); 4.30 (2H, s); 3.85 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.25 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.25 min, 331 $(M+1)^+$.

Example 76

4-[2-[(Pyrrolidin-2-oyl)amino-2-carboxy]ethyl]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.25 (2H, d); 7.67 (2H, d); 7.38 (2H, d); 7.19 (2H, d); 4.87-4.72 (2H, m); 4.27-4.21 (3H, m); 3.46-3.31 (2H, m); 3.07 (1H, dd); 2.50-2.35 (1H, m); 2.16-1.97 (3H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 7.88 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.00 min, 412 $(M+1)^+$.

Example 77

4-[(4-Carboxypiperidin-1-oyl)methyl]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.27 (2H, d); 7.68 (2H, d); 7.38 (2H, d); 7.24 (2H, d); 4.40 (1H, d); 4.27 (2H, s); 4.01 (1H, d); 3.86 (2H, s); 3.23 (1H, t); 2.93 (1H, t); 2.67-2.54 (1H, m); 2.00-1.87 (2H, m); 1.65-1.45 (2H, m). Hplc (Symmetry Rp8, Gradient 8, Water/acetonitrile/TFA) rt 5.04 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.32 min, 397 $(M+1)^+$.

Example 78

[(4-Carboxymethylpiperazin-1-oyl)methyl]phenyl-4-(aminomethyl)benzoate ditrifluoroacetate salt

^1H nmr (d_4 methanol) 8.25 (2H, d); 7.67 (2H, d); 7.37 (2H, d); 7.23 (2H, d); 4.26 (2H, s); 4.13 (2H, s); 4.03-3.86 (6H, m); 3.47-3.34 (4H, m). Hplc (Symmetry Rp8, Gradient 8, Water/acetonitrile/TFA) rt 3.90 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.07 min, 412 $(M+1)^+$.

Example 79

4-[(N-Carboxymethyl)acetamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.27 (2H, d); 7.66 (2H, d); 7.44 (2H, d); 7.21 (2H, d); 4.26 (2H, s); 3.95 (2H, s); 3.6 (2H, s). Hplc (Symmetry Rp8, Gradient 8, Water/acetonitrile/TFA) rt 4.42 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.17 min, 343 $(M+1)^+$.

Example 80

4-[(2-Carboxypyrrolidin-1-oyl)methyl]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.26 (2H, d); 7.66 (2H, d); 7.40 (2H, d); 7.21 (2H, d); 4.48 (1H, dd); 4.26 (2H, s); 3.82 (2H, s); 3.73-3.59 (2H, m); 2.35-1.98 (4H, m). Hplc (Symmetry Rp8, Gradient 8, Water/acetonitrile/TFA) rt 4.97 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.35 min, 383 $(M+1)^+$.

Example 81

4-[4-(Carboxymethyl)piperazin-1-oyl]phenyl-4-(aminomethyl)benzoate ditrifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.28 (2H, d); 7.69 (2H, d); 7.64 (2H, d); 7.42 (2H, d); 4.27 (2H, s); 4.19 (2H, s); 4.08-3.90 (4H, m); 3.56-3.44 (4H, m). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.74 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 0.80 min, 398 $(M+1)^+$.

Example 82

4-(Carboxymethyl-aminosulphonyl)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.30 (2H, d); 8.01 (2H, d); 7.71 (2H, d); 7.50 (2H, d); 4.31 (2H, s); 3.79 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt

9.04 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.20 min, 365 $(M+1)^+$.

Example 83

4-(N-Benzoylaminosulphonyl)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.33 (2H, d); 8.27 (2H, d); 7.89 (2H, d); 7.73-7.62 (3H, m); 7.59-7.50 (4H, m); 4.30 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 13.76 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.83 min, 411 $(M+1)^+$.

Example 84

4-[4-(Aminomethyl)benzoylaminosulphonyl]phenyl-4-(aminomethyl)benzoate ditrifluoroacetate salt

^1H nmr (d_4 methanol) 8.29 (2H, d); 8.21 (2H, d); 7.96 (2H, d); 7.70 (2H, d); 7.58 (2H, d); 7.52 (2H, d); 4.29 (2H, s); 4.22 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 10.44 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.12 min, 440 $(M+1)^+$.

Example 85

4-(Tetrazol-5-yl)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.24 (2H, d); 8.08 (2H, d); 7.61 (2H, d); 7.32 (2H, d); 4.21 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.81 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.17 min, 296 $(M+1)^+$.

Example 86

4-[N-(Tetrazol-5-ylmethyl)carboxamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.31 (2H, d); 8.06 (2H, d); 7.70 (2H, d); 7.43 (2H, d); 4.98 (2H, s), 4.30 (2H, s). Hplc

(Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.84 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.05 min, 353 $(M+1)^+$.

Example 87

3-[(2-Carboxy-2-acetylamino)ethyl]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.29 (2H, d); 7.69 (2H, d); 7.43 (1H, t); 7.24 (1H, d); 7.17-7.11 (2H, m); 4.73 (1H, dd); 4.29 (2H, s); 3.31 (1H, dd); 3.04 (1H, dd); 1.96 (3H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.75 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.13 min, 357 $(M+1)^+$.

Example 88

2[(2-Carboxy-2-acetylamino)ethyl]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.34 (2H, d); 7.68 (2H, d); 7.40-7.34 (2H, m); 7.30-7.20 (2H, m); 4.77 (1H, dd); 4.27 (2H, s); 3.25 (1H, dd); 2.90 (1H, dd); 1.88 (3H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.26 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.27 min, 357 $(M+1)^+$.

Example 89

2-[(Carboxymethyl)acetamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.30 (2H, d); 7.68 (2H, d); 7.51-7.39 (2H, m); 7.36-7.26 (2H, m); 4.27 (2H, s); 3.82 (2H, s); 3.65 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.42 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.20 min, 343 $(M+1)^+$.

Example 90

2-[[(1-Carboxy-2-hydroxy)ethyl]acetamido]phenyl-4-

(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.32 (2H, d); 7.68 (2H, d); 7.52-7.39 (2H, m); 7.37-7.26 (2H, m); 4.43 (1H, t); 4.28 (2H, s); 3.86 (1H, dd); 3.74 (1H, dd); 3.68 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.69 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.15 min, 373 $(M+1)^+$.

Example 91

2-[(alpha-Carboxy)benzylacetamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.25 (2H, d); 7.62 (2H, d); 7.48-7.26 (9H, m); 5.33 (1H, s); 4.27 (2H, s); 3.67 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 10.11 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.53 min, 419 $(M+1)^+$.

Example 92

2-(Carboxymethylamido)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.30 (2H, d); 7.78 (1H, d); 7.71-7.62 (3H, m); 7.46 (1H, t); 7.37 (1H, d); 4.28 (2H, s); 4.00 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 7.93 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.25 min, 329 $(M+1)^+$.

Example 93

2-[(1-Carboxy-2-hydroxy)ethylamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.29 (2H, d); 7.83 (1H, d); 7.67-7.61 (3H, m); 7.46 (1H, t); 7.36 (1H, d); 4.58 (1H, t); 4.27 (2H, s); 3.92 (1H, dd); 3,83 (1H, dd). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.44 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.03 min, 359 $(M+1)^+$.

Example 94

2-[(1-Carboxy-2-phenyl)ethylamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.19 (2H, d); 7.66-7.57 (4H, m); 7.44-7.30 (2H, m); 7.28-7.17 (5H, m); 4.78 (1H, dd); 4.28 (2H, s); 3.27 (1H, dd); 3.04 (1H, dd). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.70 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.72 min, 419 $(M+1)^+$.

Example 95

2-[N-(1(R)-Carboxy-5-aminopenyl)carboxamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.29 (2H, d); 7.78 (1H, d); 7.71-7.62 (3H, m); 7.47 (1H, t); 7.36 (1H, d); 4.51 (1H, dd); 4.29 (2H, s); 2.92-2.83 (2H, m); 2.00-1.85 (1H, m); 1.85-1.56 (3H, m); 1.56-1.39 (2H, m). Hplc (Symmetry Rp8, Gradient 7, Water/acetonitrile/TFA) rt 5.65 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.05 min, 400 $(M+1)^+$.

Example 96

2-[N-(1(S)-Carboxy-5-aminopenyl)carboxamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.28 (2H, d); 7.80-7.73 (1H, m); 7.73-7.59 (3H, m); 7.46 (1H, t); 7.35 (1H, d); 4.51 (1H, dd); 4.29 (2H, s); 2.90-2.79 (2H, m); 2.00-1.86 (1H, m); 1.86-1.57 (3H, m); 1.53-1.39 (2H, m). Hplc (Symmetry Rp8, Gradient 7, Water/acetonitrile/TFA) rt 4.37 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.08 min, 400 $(M+1)^+$.

Example 97

[4-Chloro-2-(carboxymethyl)amido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.28 (2H, d); 7.79 (1H, d); 7.69-7.62 (3H, m); 7.39 (1H, d); 4.28 (2H, s); 3.99 (2H, s).

Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 9.45 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.28 min, 363 $(M+1)^+$.

Example 98

[4-Chloro-2-(1-carboxy-2-hydroxy)ethylamido]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.29 (2H, d); 7.84 (1H, d); 7.68-7.61 (3H, m); 7.39 (1H, d); 4.57 (1H, t); 4.27 (2H, s); 3.92 (1H, dd); 3.84 (1H, dd). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 8.85 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.30 min, 393 $(M+1)^+$.

Example 99

[4-Chloro-2-[(1-carboxy-2-phenyl)ethylamido]]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.14 (2H, d); 7.63-7.51 (4H, m); 7.32 (1H, d); 7.26-7.15 (5H, m); 4.73 (1H, dd); 4.25 (2H, s); 3.25 (1H, dd); 3.00 (1H, dd). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 10.59 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 2.75 min, 453 $(M+1)^+$.

Example 100

[4-Chloro-2-[(alpha-carboxy)benzylamido]]phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^1H nmr (d_4 methanol) 8.18 (2H, d); 7.77 (1H, d); 7.66-7.60 (3H, m); 7.39-7.29 (6H, d); 5.52 (1H, s); 4.29 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 10.45 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.77 min, 439 $(M+1)^+$.

Example 101

2-(Tetrazol-5-yl)phenyl-4-(aminomethyl)benzoate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.27 (2H, d); 8.00 (1H, d); 7.75 (1H, t); 7.67 (2H, d); 7.62-7.50 (2H, m); 4.29 (2H, s). Hplc (Magellan C8, Gradient 5, Water/acetonitrile/TFA) rt 10.26 min. LC/MS (Magellan C18 Gradient 6, water/acetonitrile/TFA) rt 1.37 min, 296 $(M+1)^+$.

Example 102

Phenyl 4-(aminomethyl)-2-methylbenzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.25 (1H, d); 7.54-7.47 (4H, m); 7.38-7.32 (1H, m); 7.30-7.25 (2H, m); 4.24 (2H, s); 2.74 (3H, s). M.S. TOF 242 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 9.69 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 9.91 min.

Example 103

Phenyl 4-(aminomethyl)-3-methylbenzoate hydrochloride salt

^{1}H nmr (d_4 methanol) 8.17-7.75 (2H, m); 7.62 (1H, d); 7.51 (2H, t); 7.35 (1H, t); 7.27 (2H, d); 4.32 (2H, s); 2.57 (3H, s). M.S. TOF 242 $(M+1)^+$. Hplc (Jupiter5 C18, Gradient 1, Water/acetonitrile/TFA) rt 9.40 min. Hplc (SymmetryC8 Gradient 2, Water/acetonitrile/TFA) rt 9.82 min.

References

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Protocol for Tryptase Inhibition Assay

Tryptase assays were carried out at room temperature in 0.1 M phosphate buffer, 0.5 mg/ml heparin, pH 7.4 according to a method of Tapparelli et

al. (1993)*J.Biol.Chem.* 268, 4734-4741. Purified human lung tryptase was purchased from Dr Andrew Walls, Immunopharmacology Group, Southampton General Hospital, Southampton, UK. The chromogenic substrate for tryptase, S-2366, was purchased from Quadratech, Epsom, Surrey, UK. Product (p-nitroaniline) was quantified by absorption at 405nm in 96 well microplates using a Dynatech MR 5000 reader (Dynex Ltd, Billingshurst, UK). K_m and K_i were calculated using SAS software. A K_m value of 216μM was determined for tryptase/S-2366. Inhibitor stock solutions were prepared at 40 mM in Me_2SO and tested within the range 100mM-1nM. Accuracy of K_i measurements was confirmed by comparison with K_i values of a known inhibitor of tryptase. In agreement with published data, benzamidine inhibited tryptase with a K_i value of 30μM.

The tryptase pKi's of a number of the compounds of the invention are illustrated in Table 1 below. Also quoted are the trypsin pKi's of the compounds.

Table 1

Ex. No.	Ar	pK_i tryptase	pK_i trypsin
10	4-Cyanophenyl	9.22	7.99
16	6-quinolyl	8.33	7.48
24	6'-carboxymethyl-2-naphthyl	8.17	7.42

In all cases R and Y represent hydrogen in formula (I).

These results clearly illustrate the efficacy of the compounds of the invention as well as their selectivity for tryptase over the serine protease trypsin.

Protocol for assessment of plasma stability.

The stability of compounds on incubation in human plasma

can be used to demonstrate the hydrolytic stability of the ester moiety towards the range of esterases and proteases normally present in plasma. As such, this assay is an informative measure of metabolic stability in the whole animal for compounds where ester hydrolysis is a major metabolic pathway.

In general, 10 uM samples of compound were incubated at 37 C in 3 ml human plasma. Aliquots were removed at intervals over a 4 hour incubation, extracted by solid phase techniques and analysed by HPLC.

The half-life of hydrolysis of some representative esters are illustrated in Table 2 below.

Table 2

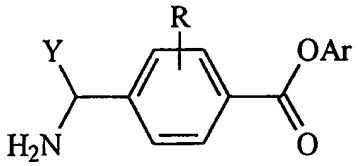
Ex. No.	Ar	t1/2 of hydrolysis on plasma incubation
10	4-cyanophenyl	< 5 minutes
57	4-[4-Carboxy piperidin-1-oyl] phenyl	107 min
52	4-[(2-Acetylamino-2-carboxy)ethyl] phenyl	22 hours

In all cases R and Y represent hydrogen in formula (I).

These results indicate that the stability to hydrolysis by plasma enzymes is greatly enhanced for some compounds, which may therefore be preferred for therapeutic appliction, particularly for systemic adminstration.

Claims

1. Use of a tryptase inhibitor of formula I



(I)

wherein R represents hydrogen, alkyl, alkenyl, hydroxy, alkoxy, aminoalkyl, hydroxyalkyl, carboxyalkyl, alkoxyalkyl, amino, halo, cyano, nitro, thiol, alkylthio, haloalkoxy or haloalkyl;

Ar represents an optionally substituted carbocyclic or heterocyclic aryl group with the proviso that when Ar represents a naphthyl moiety it is not substituted by amidino or guanidine; and

Y represents a hydrogen atom or alkyl group;

or a physiologically tolerable salt thereof;

in the manufacture of a medicament for use in a method of treatment of the human or non-human animal body to combat a condition responsive to said inhibitor.

2. Use as claimed in claim 1 wherein Y represents hydrogen.

3. Use as claimed in either one of claims 1 or 2 wherein R represents hydrogen.

4. Use as claimed in any one of claims 1 to 3 wherein Ar represents optionally subsituted phenyl, naphthyl, pyridyl, quinolyl or isoquinolyl.

5. Use as claimed in claim 4 wherein Ar represents a phenyl or naphthyl group substituted by one or more substituents selected from: halo, methylenedioxy, $-R^1$,

$-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCO_2R^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w$-Ph, or R^1 and R^2 are optionally connected by a bond to form a 5-8 atom cyclic structure or connected via an O, S or N atom to form a 5-8 atom heterocyclic structure and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; R^3 is an oligomer comprising 1-4 aminoacid monomers, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2.

6. Use as claimed in claim 5 wherein Ar is substituted by an electron-withdrawing group and/or a protected or unprotected acidic group.

7. Use as claimed in claim 6 wherein said electron withdrawing group is selected from cyano, nitro, carboxamido, alkylsulfenyl, alkylsulfonyl, alkylaminosulfonyl, trifluoromethyl or halogen.

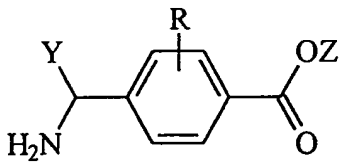
8. Use as claimed in claim 6 or 7 wherein said acidic group is selected from alkyl or aryl carboxylic acids and esters, acyl sulphonamide, sulphonylamidocarboxyalkyl, carboxyamidosulphonylalkyl, tetrazole, sulphonic acid or phosphonic acid each bonded to the Ar ring directly or via an alkyl, sulphonamidoalkyl or carboxamidoalkyl linkage, the linkage itself being optionally substituted by C_{1-4}

alkyl, CN, NO_2, NH_2, NHCO-alkyl, or halogen.

9. Use as claimed in claim 8 wherein if Ar is a phenyl derivative then said acidic substituent is present on the para position of the phenyl ring.

10. Use as claimed in claim 8 wherein if Ar is phenyl said acidic substituent is present on the ortho position and said electron withdrawing substituent is present on the para position of the phenyl ring.

11. A compound of formula (II)



(II)

wherein R represents hydrogen, alkyl, alkenyl, hydroxy, alkoxy, aminoalkyl, hydroxyalkyl, carboxyalkyl, alkoxyalkyl, amino, halo, cyano, nitro, thiol, alkylthio, haloalkoxy or haloalkyl;

Y represents a hydrogen atom or alkyl group;; and

Z represents a phenyl group substituted by methylenedioxy, $-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w-Ph$, or R^1 and R^2 are optionally connected by a bond to form a 5-8 atom cyclic structure (eg. piperidine) or connected via an O, S or N atom to form a 5-8 atom heterocyclic

structure (eg. morpholine, piperazine) and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; where R^3 is an oligomer comprising 1-4 aminoacid monomers, such as the natural aminoacids glycine, proline and serine, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2; or

Z represents a phenyl group subsituted in the 2-position by nitro or in the 3-position by methoxy; or

Z represents a naphthyl group substituted by halo, methylenedioxy, $-R^1$, $-NR^1COR^2$, C_{2-6}-alkenyl, $-(CH_2)_w-OR^1$, $-(C_{1-6})$-perfluoroalkyl, $-(CH_2)_wCN$, $-(CH_2)_wNO_2$, $-(CH_2)_wCF_3$, $-(CH_2)_wS(O)_rR^1$, $-(CH_2)_wNR^1R^2$, $-(CH_2)_wCOR^1$, $-(CH_2)_wCO_2R^1$, $-(CH_2)_wCONR^1R^2$, $-(CH_2)_wSO_2NR^1R^2$, $-(CH_2)_wNHSO_2R^1$, $-(CH_2)_wNHCOR^1$, $-(CH_2)_wNHCO_2R^1$, $-OC(=O)R^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-P(O)_{2-3}-R^1$, $-(CH_2)_w-C(=O)-R^3$ and optionally substituted aryl where R^1 and R^2 independently represent H, C_{1-8} alkyl, C_{3-7} cycloalkyl, or $-(CH_2)_w-Ph$, or R^1 and R^2 are optionally connected by a bond to form a 5-8 atom cyclic structure or connected via an O, S or N atom to form a 5-8 atom heterocyclic structure and where R^1 and/or R^2 are also optionally substituted with $-(CH_2)_w-COOR^1$, $-(CH_2)_w-CH(NHCOR^1)-COOR^2$, $-(CH_2)_w-CH(NR^1R^2)-COOR^1$, $-(CH_2)_w-CONH-SO_2-R^1$, $-(CH_2)_w-SO_2-NHCO-R^1$, $-(CH_2)_w$-tetrazole, $-(CH_2)_w-S(O)_r-R^1$, or $-(CH_2)_w-P(O)_{2-3}-R^1$; where R^3 is an oligomer comprising 1-4 aminoacid monomers, terminated by a free carboxylic acid, ester or amide functionality; and w=0-5 and r=0-2; or

a heterocyclic aryl groups containing 5 to 10 ring atoms including 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur; or

a physiologically tolerable salt thereof.

12. A compound of formula (II) as claimed in claim 11

for use in combatting a condition responsive to said inhibitor.

13. A pharmaceutical composition comprising a compound of formula (II) as claimed in claim 11, together with at least one pharmaceutically acceptable excipient.

14. A pharmaceutical composition comprising a compound of formula (I) as claimed in claims 1 to 10, together with one or more anti-asthma agents and at least one pharmaceutically acceptable excipient.

15. A method of treatment of human or non-human animal body to combat a condition responsive to a tryptase inhibitor, said method comprising administering to said body an effective amount of a tryptase inhibitor as claimed in any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB 99/01263

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/38 A61K31/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARTIN POE ET AL.: "The enzymatic activity of human cytotoxic T-Lymphocyte Granzyme A and ...." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 284, no. 1, January 1991 (1991-01), pages 215-218, XP002110066 NEW YORK, US, US ISSN: 0003-9861 the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 1999	06/08/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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